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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/580,329

05/24/2006

Qiu-Ping Qin

OHMAN-010

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7590

07/07/2009

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ALEXANDRIA, VA 22314

EXAMINER

GRUN, JAMES LESLIE

ART UNIT

PAPER NUMBER

1641

MAIL DATE

DELIVERY MODE

07/07/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/580,329	Applicant(s) QIN ET AL.	
	Examiner JAMES L. GRUN	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 April 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17-22,25-28,30,33 and 34 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17-22,25-28,30,33 and 34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>4/16/09</u> . | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1641

The amendment filed 16 April 2009 is acknowledged and has been entered. Claims 1-16, 23, 24, 29, 31, and 32 have been cancelled. Claims 17-22, 25-28, 30, 33, and 34 remain in the case.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Claims 17-22, 25-28, 30, 33, and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Absent further written description and guidance from applicant, one would not know or be able to predict what other “binders” specifically bind to the pregnancy-associated plasma protein-A (PAPP-A) complexed or not complexed with pro major basic protein (proMBP) and predictably function in the assay other than specific antibodies for PAPP-A or proMBP.

Art Unit: 1641

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics when coupled with a known or disclosed structure/function correlation, methods of making the claimed product, or any combination thereof. The specification does not provide sufficient recitation of distinguishing identifying characteristics of the genus of “binders” other than for antibody populations specific for the PAPP-A or the proMBP components of the PAPP-A/proMBP complexes. Moreover, applicant does not teach an antibody that binds to PAPP-A only when complexed to proMBP, the specification teaches antibodies that bind to proMBP whether it is complexed to PAPP-A and/or angiotensinogen and/or complement C3dg (see e.g. Christiansen et al. (Clin. Chem. 46: 1099, 200)).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of binders and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

Art Unit: 1641

See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Furthermore, In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement that defines a genus of molecules by only their functional activity does not provide an adequate written description of the genus. The court indicated that although applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules falling within the scope of the claimed genus.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). However, in view of the guidance in the instant specification only to antibodies which function as binders for PAPP-A or the proMBP components of the PAPP-A/proMBP complexes as intended by applicant, the amount of experimentation required to determine functional structures or modifications for other usable binders would also be undue. Note that an enabling disclosure for the preparation and use of only a few analogs of a product does not enable all possible analogs where the characteristics of the analogs are unpredictable. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* (18 USPQ 2d 1027 (CAFC 1991)).

Therefore, only antibodies binding to PAPP-A or the proMBP components of the PAPP-A/proMBP complexes, but not the full breadth of the claims, meet the written description and enablement provisions of 35 U.S.C. §112, first paragraph.

Art Unit: 1641

Claim 17 and claims dependent thereupon are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with that as claimed.

Applicant teaches adsorption of PAPP-A/proMBP complexes with an antibody specific for proMBP prior to assay for PAPP-A as a method of removing the complexes from participation in the PAPP-A assay. Applicant suggests blocking as an alternative method of making complexes “non-capable of participating” in a PAPP-A assay, but does not provide evidence that antibody pairs exist or can be isolated that function to block and remove complexes from participation (see e.g. page 8). Applicant provides no other guidance as to how one makes complexes “non-capable of participating” in a PAPP-A assay. In the absence of sufficient guidance to antibody pairs that function for total blocking or any other means of making complexes “non-capable of participating” in a PAPP-A assay, one would not be assured of the ability to practice the method with other than adsorption with anti-proMBP antibodies for prior removal of the complexes. Applicant’s specification provides a mere suggestion to one in the art to perform further random unpredictable experimentation to determine with which means and conditions one could achieve the desired goal of making complexes “non-capable of participating” in a PAPP-A assay. Such an invitation to experiment does not provide an indication that applicant had possession of the invention of the scope as claimed at the time the application was filed and does not provide an enabling disclosure.

Art Unit: 1641

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-22, 25-28, 30, 33, and 34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 and claims dependent thereupon are method claims and, as such, they should clearly set forth the various method steps in a positive, sequential manner using active tense verbs such as mixing, reacting, and detecting. Again, with regard to the deficiencies noted above, it is unclear how one performs any measurement of PAPP-A with the method as instantly claimed in alternative “ii)” because sample is merely exposed to binder and it is not clear that sufficient active, positive steps are set forth delimiting how the method is actually practiced. In these claims, “the” bioaffinity reaction lacks antecedent basis and it is not clear in which assay the reaction occurs, e.g. in the assay of the preamble or in the direct assay.

In claim 22, recitations of “using” or variations thereof are not valid method steps.

In claim 25, the interrelationships of the steps and components of the method are not clear, e.g. it is not clear how blocking or pre-adsorption relate to detecting PAPP-A complexed to proMBP.

In claim 26, “the” immunoassay lacks antecedent basis. It is also unclear which of the recited binders is “the” binder.

Claim 27 and claims dependent thereupon are method claims and, as such, they should clearly set forth the various method steps in a positive, sequential manner using active tense verbs such as mixing, reacting, and detecting. Claims 28, 30, 33, and 34, in particular, are

Art Unit: 1641

indefinite because without sufficient active, positive steps delimiting how the method is actually practiced it is unclear what method/process applicant is intending to encompass. The interrelationships of the steps and components of the method, and the purpose of the method, are not clear, e.g. it is not clear what is being diagnosed, acute coronary syndrome or a risk therefor.

Applicant's arguments filed 16 April 2009 have been fully considered but they are not deemed to be persuasive. Notwithstanding applicant's assertions to the contrary, applicant's amendments have not obviated rejections under this statute for the reasons set forth above.

Claim 17 and claims dependent thereupon are objected to because of the following informalities: --PAPP-A-- should be recited in alternative "i)" rather than "PAAP-A".

Appropriate correction is required.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent,

except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language;

Claims 17 and 26 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Overgaard et al. (WO 00/54806).

Art Unit: 1641

Overgaard et al. teach the production of monoclonal antibodies specific for pregnancy-associated plasma protein-A (PAPP-A) not complexed with pro major basic protein (proMBP) and the use of the antibodies for detection of uncomplexed PAPP-A in a sample (see e.g. page 6). The reference also teaches that recombinant PAPP-A can be produced in cells devoid of proMBP production, such as human embryonic kidney 293T cells, and detected with available antibodies specific for PAPP-A that also bind PAPP-A/proMBP complexes (see e.g. pages 6-7 and 28). Expression of recombinant PAPP-A in a human cell that does not produce proMBP and assay of culture supernatant fluid, i.e. a person's sample, is considered herein as making complexes "non-capable of participating" in the PAPP-A assay.

Claims 17 and 26 are rejected under 35 U.S.C. § 102(e)(2) as being clearly anticipated by Overgaard et al. (US 7,115,382).

Overgaard et al. teach the production of monoclonal antibodies specific for pregnancy-associated plasma protein-A (PAPP-A) not complexed with pro major basic protein (proMBP) and the use of the antibodies for detection of uncomplexed PAPP-A in a sample (see e.g. col. 5 and Claim 1). The reference also teaches that recombinant PAPP-A can be produced in cells devoid of proMBP production, such as human embryonic kidney 293T cells, and detected with available antibodies specific for PAPP-A (see e.g. cols. 5-6 and 22-23). Expression of recombinant PAPP-A in a human cell that does not produce proMBP and assay of culture supernatant fluid, i.e. a person's sample, is considered herein as making complexes "non-capable of participating" in the PAPP-A assay.

Art Unit: 1641

Claims 27 and 28 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Conover et al. (US 6,500,630) for reasons of record. As set forth, the reference teaches: determinations of pregnancy-associated plasma protein-A (PAPP-A) as a marker for inflammatory conditions, in particular acute coronary syndromes; the production of monoclonal antibodies specific for PAPP-A not complexed with pro major basic protein (proMBP) and the use of the antibodies for detection of uncomplexed PAPP-A in a sample (see e.g. cols. 4 and 6); and, an assay for PAPP-A activity, inherently measuring the free active form, wherein the enzyme is captured with an antibody and reacted with substrate (see e.g. col. 7).

Applicant's arguments and the declaration under 37 CFR 1.132 of Dr. Kim Pettersson filed 16 April 2009 have been fully considered but they are not deemed to be persuasive.

Notwithstanding applicant's assertions to the contrary in the declaration of Dr. Pettersson and in applicant's response, the disclosure of Conover et al. is not limited to that which is specifically exemplified in view of the disclosures regarding immunization with uncomplexed recombinant PAPP-A and the additional passage noted in the rejection of record at column 6: "Antibodies having affinity for PAPP-A are identified in a positive selection. Antibodies identified in such a selection can be negatively selected against PAPP-A/proMBP, to identify antibodies having specific binding affinity for epitopes of PAPP-A that are not accessible in the specific complex of PAPP-A and proMBP." Moreover, as admitted in the declaration and in applicant's response, the method specifically exemplified in the reference clearly detects free PAPP-A and the rise in PAPP-A concentrations detected in the patients in the reference is inherently the result of a rise in free PAPP-A concentrations in the non-pregnant ACS patients. Applicant's assertions and those of Dr. Pettersson in the declaration regarding the lack of

Art Unit: 1641

specificity of an enzymatic antibody capture assay for the detection of free PAPP-A were not found persuasive in view of the above noted teachings regarding antibody selection and the well known inhibition of PAPP-A enzymatic activity when complexed with proMBP (see e.g. cols. 4 and/or 5). The rejection is maintained for the reasons of record.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Overgaard et al. (JBC 275: 31128, 2000) teach proMBP as an inhibitor of PAPP-A enzymatic activity.

Christiansen et al. (Clin. Chem. 46: 1099, 200) teach detection of angiotensinogen /proMBP complexes.

Art Unit: 1641

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 11 a.m. to 7 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, SPE, can be contacted at (571) 272-0806.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/J. L. G./

James L. Grun, Ph.D.

Examiner, Art Unit 1641

July 6, 2009

/Ann Y. Lam/

Primary Examiner, Art Unit 1641

July 2, 2009